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Distinct Representations of Cognitive and Motivational Signals in Midbrain Dopamine Neurons

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SUMMARY

Dopamine is essential to cognitive functions. However, despite abundant studies demonstrating that dopamine neuron activity is related to reinforcement and motivation, little is known about what signals dopamine neurons convey to promote cognitive processing. We therefore examined dopamine neuron activity in monkeys performing a delayed matching-to-sample task that required working memory and visual search. We found that dopamine neurons responded to task events associated with cognitive operations. A subset of dopamine neurons were activated by visual stimuli if the monkey had to store the stimuli in working memory. These neurons were located dorsolaterally in the substantia nigra pars compacta, whereas ventromedial dopamine neurons, some in the ventral tegmental area, represented reward prediction signals. Furthermore, dopamine neurons monitored visual search performance, becoming active when the monkey made an internal judgment that the search was successfully completed. Our findings suggest an anatomical gradient of dopamine signals along the dorsolateral-ventromedial axis of the ventral midbrain.

INTRODUCTION

Dopamine neurons in the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) are well known for their crucial roles in reward processing (Schultz, 1998; Wise, 2004). These neurons are excited by reward or sensory cue predicting reward if the reward value is higher than expected, while they are inhibited if the value is lower than expected (Bayer and Glimcher, 2005; Morris et al., 2004; Nakahara et al., 2004; Nomoto et al., 2010; Satoh et al., 2003; Schultz, 1998). This response property led to a hypothesis that dopamine neurons encode reward prediction error that indicates a discrepancy between expected and actual reward values (Doya, 2002; Montague et al., 1996; Schultz et al., 1997). Such a value-related signal is proposed to play important roles as a teaching signal in reinforcement learning (Doya, 2002; Montague et al., 1996; Schultz et al., 1997) and as an incentive signal in reward seeking behavior (Berridge and Robinson, 1998).

In contrast to their accepted role in reward processing, there has been considerable debate over the role of dopamine neurons in processing nonrewarding events. Some theories suggest that dopamine neurons primarily signal rewarding events (Schultz, 1998; Ungless, 2004), while others suggest that they encode additional signals related to surprising, novel, salient, and even aversive experiences (Bromberg-Martin et al., 2010b; Horvitz, 2000; Redgrave and Gurney, 2006). Supporting the latter theories, recent studies reported that, although a group of dopamine neurons was inhibited by aversive events as they encoded the value-related signal, another group of dopamine neurons was excited (Brischoux et al., 2009; Guarraci and Kapp, 1999; Matsumoto and Hikosaka, 2009). Since the neurons with excitatory responses to aversive events were excited by rewarding events as well, they were presumed to encode motivational salience rather than motivational value (Matsumoto and Hikosaka, 2009). Based on these findings, it was proposed that dopamine neurons are not a homogeneous population and are divided into multiple groups encoding distinct signals suitable for different functions (Bromberg-Martin et al., 2010b).

Consistent with the idea, the dopamine system is involved in multiple functions. Especially, dopamine released in the prefrontal cortex (PFC) has been implicated in cognitive processing rather than motivational functions (Nieoullon, 2002; Robbins and Arnsten, 2009), including attentional selection (Crofts et al., 2001; Robbins and Roberts, 2007), saccade target selection (Noudoost and Moore, 2011), and performance monitoring (Ullsperger, 2010; Vezoli and Procyk, 2009). In particular, a prominent role in working memory has been established. Extracellular dopamine level increases in the dorsolateral prefrontal cortex (dlPFC) during working memory performance (Watanabe et al., 1997), and the blockade of dopamine D1 receptors in the dlPFC impairs working memory (Li and Mei, 1994; Sawaguchi and Goldman-Rakic, 1991, 1994). An electrophysiological study in monkeys performing spatial working memory tasks also

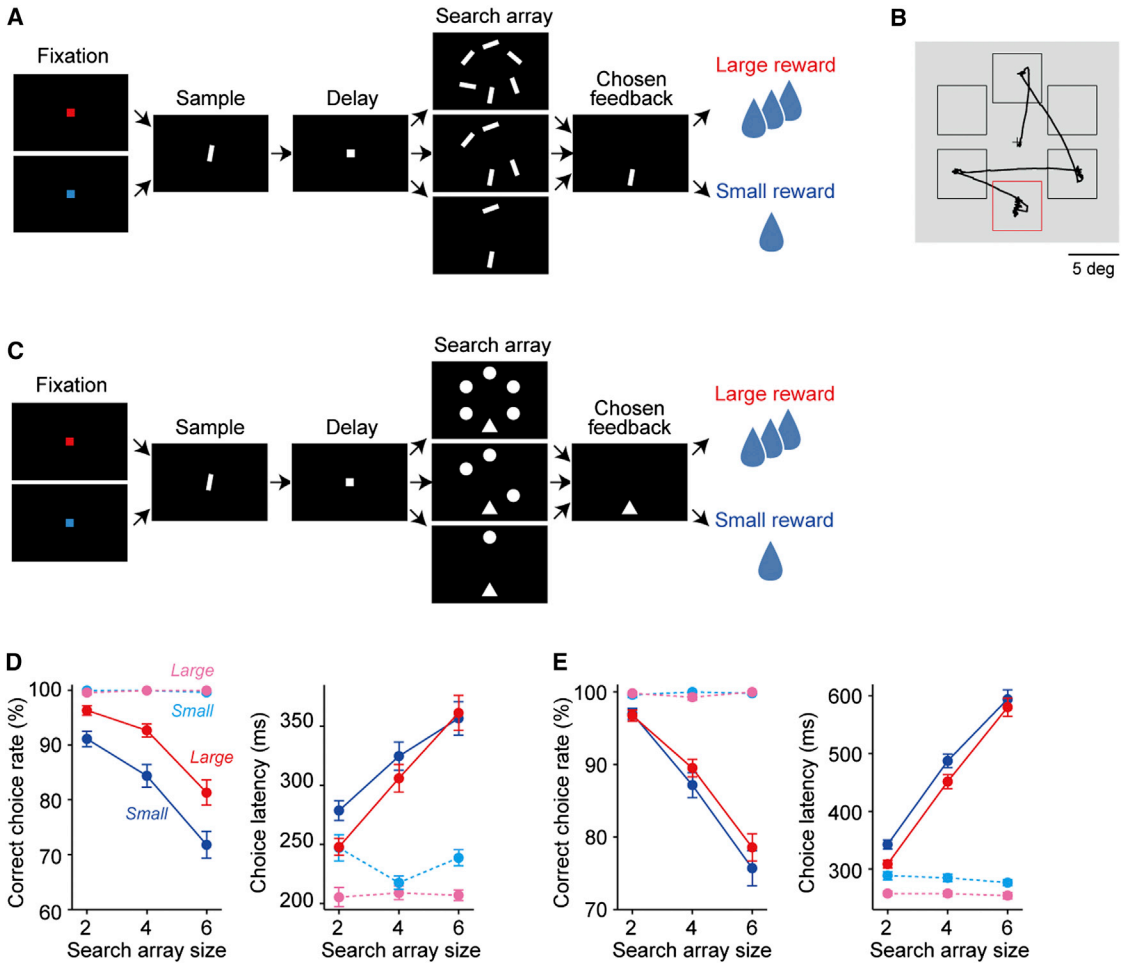

Figure 1. Behavioral Task and Performance

(A) DMS task.

(B) Eye movement during visual search in a six-size array trial of the DMS task. Red square indicates the fixation window of a matching target. Black squares indicate the windows of each distractor.

(C) Control task.

(D) Correct choice rate (left) and choice latency (right) plotted against the search array size in monkey F, shown for the large reward trials (red) and the small reward trials (blue) in the DMS task, and the large reward trials (magenta) and the small reward trials (cyan) in the control task. Error bars indicate SEM.

(E) Correct choice rate and choice latency in monkey E.

See also Figure S1.

reported consistent data showing that the blockade of dopamine D1 receptors attenuates the spatially tuned persistent firing of dlPFC neurons (Williams and Goldman-Rakic, 1995). Dopamine is therefore essential to prefrontal cognitive functions. These findings have inspired hypotheses about what signals dopamine neurons might convey to the PFC to support these cognitive functions (Cohen et al., 2002; Durstewitz et al., 2000).

However, despite the wealth of studies demonstrating that dopamine neuron signals are related to reinforcement and motivation, little is known about whether dopamine neurons convey signals suitable for promoting cognitive processing. In the present study, we aimed at identifying the signals carried by dopamine neurons when monkeys were engaged in a cognitive task. Specifically, we recorded single-unit activity from dopamine neurons in the ventral midbrain, including the SNc and VTA, while monkeys were performing a delayed matching-to-sample (DMS) task that required working memory and visual search. We found that the activity of dopamine neurons at different locations within the ventral midbrain reflected signals suitable for distinct roles in cognitive processing.

RESULTS

Delayed Matching-to-Sample Task and Behavioral Performance

We trained two monkeys (monkey F and monkey E) to perform a DMS task (Figure 1A). Each trial began with the presentation of a colored fixation point. The color indicated the magnitude of reward (large or small) that the monkey would obtain after correct performance of the trial. While the monkey was fixating the point,

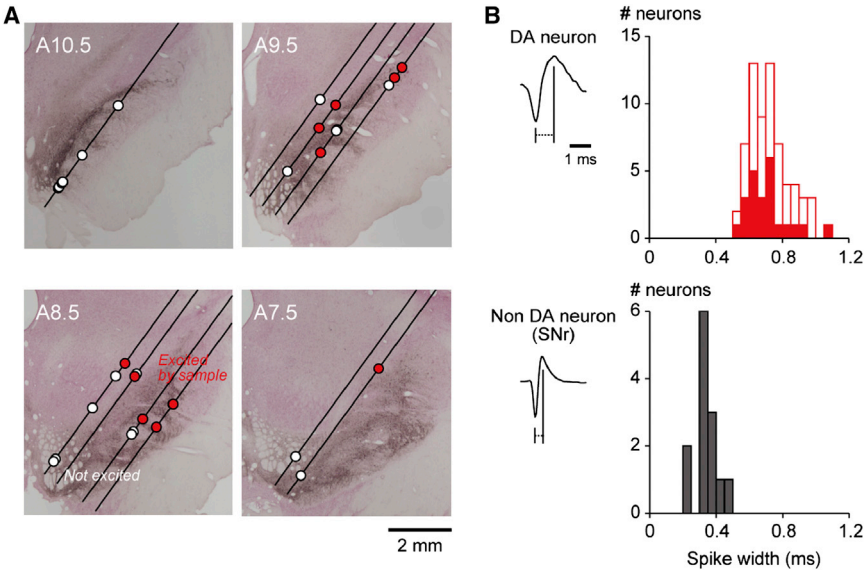

Figure 2. Histological Reconstruction of Recording Sites

(A) Recording sites of 31 dopamine neurons in monkey F. Red circles indicate dopamine neurons showing a significant excitation to the sample stimulus in the large reward trials during the DMS task ($p < 0.05$, Wilcoxon signed-rank test).

(B) Distributions of the spike durations of the recorded dopamine neurons (top) and SNr neurons (bottom). Filled red bars indicate neurons showing a significant excitation to the sample stimulus ($p < 0.05$, Wilcoxon signed-rank test). Example spike shapes for each neuron type are shown on the left. The two vertical lines indicate how the spike duration was measured.

a visual object (tilted bar) was presented as a sample. The monkey had to remember the sample. After a delay period, a search array with two to six bars, one of which matched the sample, was presented. The monkey was required to find the matching target. No constraints were placed on eye position during search behavior, so that the monkey could make several saccades (Figure 1B). The monkey had to indicate the target that had been found, by fixating it for a certain period (550 ms for monkey F and 750 ms for monkey E, see Figure S1 online for the time during which the monkey gazed at a distracter before choosing the matching target) to obtain a juice reward. The sample was behaviorally relevant in the DMS task, whereas it was made irrelevant in a control task (Figure 1C). Thus, the search arrays in the control task were composed of two to six objects: one of them was a triangle, and the others were circles. The task was just to choose the pop-out triangle irrespective of what the sample was. The DMS and control tasks were run in separate blocks of trials.

Behavioral performance was influenced by the expected reward magnitude and the search array size (Figures 1D and 1E for monkeys F and E, respectively). Correct choice rate in the DMS task was higher in the large reward trials than in the small reward trials in both monkeys, though the difference was significant only in monkey F (monkey F, $p < 0.01$; monkey E, $p = 0.15$; Fisher's exact probability two-tailed test). The correct choice rate was decreased as the search array size increased (correlation between correct choice rate and array size; monkey F, large reward trials, $r = -0.57$, $p < 0.01$, small reward trials, $r = -0.58$, $p < 0.01$; monkey E, large reward trials, $r = -0.68$, $p < 0.01$, small reward trials, $r = -0.64$, $p < 0.01$). These data indicate that the monkey's performance was facilitated when the large reward was expected, while it was reduced when the search array size was larger. Consistent with this interpretation, the time taken to find the target (choice latency) was significantly shorter in the large reward trials (monkeys F and E, $p < 0.01$, Wilcoxon rank-sum test) and increased as the search array size increased (correlation between choice latency and array size; monkey F, large reward trials, $r = 0.21$, $p < 0.01$, small reward trials, $r = 0.15$, $p < 0.01$; monkey E, large reward trials, $r = 0.38$, $p < 0.01$, small reward trials, $r = 0.35$, $p < 0.01$). On the other hand, correct choice rate in the control task was almost 100% and was not influenced by the reward magnitude (monkeys F and E, $p > 0.05$, Fisher's exact probability two-tailed test) or the search array size (correlation between correct choice rate and array size; monkey F, large reward trials, $r = 0.16$, $p > 0.05$, small reward trials, $r = -0.16$, $p > 0.05$; monkey E, large reward trials, $r = 0.05$, $p > 0.05$, small reward trials, $r = 0.07$, $p > 0.05$). However, choice latency was significantly shorter in the large reward trials (monkeys F and E, $p < 0.01$, Wilcoxon rank-sum test), although it was not influenced by the search array size (correlation between choice latency and array size; monkey F, large reward trials, $r = 0.01$, $p > 0.05$, small reward trials, $r = -0.03$, $p > 0.05$; monkey E, large reward trials, $r = -0.02$, $p > 0.05$, small reward trials, $r = -0.04$, $p > 0.05$). These data suggest that the monkey's performance in the control task was facilitated when the large reward was expected, though it was not influenced by the number of distracter stimuli.

Representation of Reward Magnitude in Dopamine Neurons

While the monkeys were performing the DMS task, we recorded single-unit activity from 66 putative dopamine neurons (31 in monkey F and 35 in monkey E) in the ventral midbrain including the SNc and VTA (Figure 2A). Of these, 50 neurons were also examined using the control task. We identified dopamine neurons on the basis of the following electrophysiological criteria: a low background firing rate around five spikes/s (mean ± SD = 4.7 ± 1.4 spikes/s), a broad spike waveform in clear contrast to neighboring neurons with a high background firing rate in the substantia nigra pars reticulata (Figure 2B), and a phasic increase in discharge caused by an unexpectedly delivered reward. We henceforth call them dopamine neurons.

We first examined the response of dopamine neurons to the fixation point predicting large or small reward (Figure 3). As reported before, many of the recorded neurons were strongly excited by the large reward cue, and their response to the small reward cue was much smaller (see Figure 3A for an example

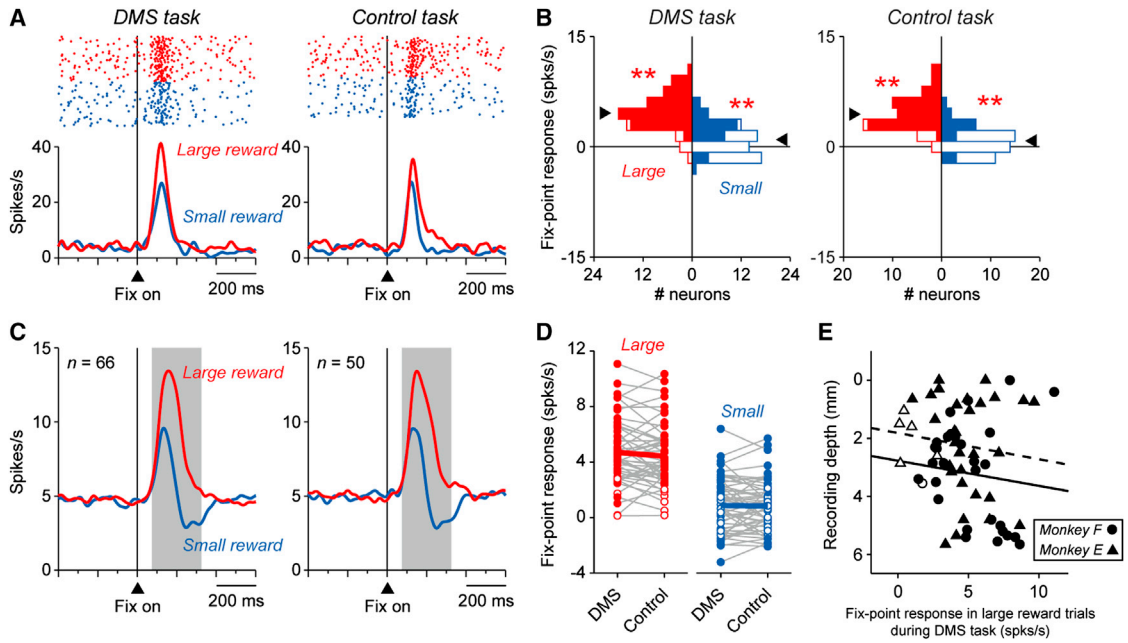

Figure 3. Response of Dopamine Neurons to the Fixation Point Predicting Reward Magnitude

(A) Activity of an example dopamine neuron in the DMS task (left) and the control task (right). Rasters and spike density functions (SDFs) are aligned by fixation point onset and shown for the large reward trials (red) and the small reward trials (blue).

(B) Distributions of the response magnitudes of the 66 neurons recorded in the DMS task (left) and the 50 neurons recorded in the control task (right). They are shown for the large reward trials (red) and the small reward trials (blue). Filled bars indicate neurons showing a significant response ($p < 0.05$, Wilcoxon signed-rank test). Arrows indicate the mean of the response magnitude. Double asterisks indicate a significant deviation from zero ($p < 0.01$, Wilcoxon signed-rank test).

(C) Averaged activities of the 66 neurons recorded in the DMS task (left) and the 50 neurons recorded in the control task (right). SDFs are shown for the large reward trials (red) and the small reward trials (blue). Gray area indicates the period that was used to analyze the response to the fixation point.

(D) Changes in the response magnitudes between the DMS task and the control task for each neuron recorded using both tasks (n = 50). They are shown for the large reward trials (red) and the small reward trials (blue). Each pair of circles connected by a gray line indicates the data of each neuron. Colored thick lines indicate changes in the mean of the response magnitude. Filled circles indicate neurons showing a significant response ($p < 0.05$, Wilcoxon signed-rank test).

(E) Relation between the recording depth and the response magnitude to the fixation point predicting the large reward in the DMS task for each monkey (circles and continuous regression line for monkey F, and triangles and dashed regression line for monkey E). The recording depth was measured from a reference depth (the recording depth of the shallowest dopamine neuron for each monkey). Filled circles indicate neurons showing a significant response ($p < 0.05$, Wilcoxon signed-rank test).

See also Figures S3, S4A, and S5.

dopamine neuron activity, Figure 3B for the response magnitudes of each neuron, and Figure 3C for averaged activity). Overall, these responses were almost identical in the two tasks. This is made evident by the comparison of the response magnitude for each neuron (Figure 3D), as there was no significant difference in the response magnitudes between the DMS and control tasks for each reward size ($p > 0.05$, Wilcoxon signed-rank test). These data are consistent with the hypothesis that dopamine neurons encode a value-related signal that is high for large reward and low for small reward, regardless of the different task contexts.

Modulation of Dopamine Neuron Activity by Working Memory Demand

We next analyzed the response to the sample stimulus (Figure 4). If dopamine neurons encode only reward-related information such as reward prediction errors, then they should not have any response to the sample stimulus, because it does not provide any new information about the size or probability of future reward. On the other hand, if the activity of dopamine neurons is influenced by the cognitive demand of the sample stimulus, such firing pattern may not be accounted for by a simple reward prediction error framework.

An example neuron showed an excitation to the sample in the DMS task (Figure 4A). This excitation occurred in both the large and the small reward trials. On the other hand, the excitation was attenuated in the control task in which the sample was not relevant to the task. Thus, this neuron was excited when the monkey had to attend to the sample and store it in working memory, but it showed little response to the same stimulus when it was no longer behaviorally relevant.

As a population, the sample response was significantly positive in both the large and the small reward trials in the DMS task (n = 66, $p < 0.01$, Wilcoxon signed-rank test) (Figure 4B, left), while it was not significantly different from zero in the control task (n = 50, $p > 0.05$, Wilcoxon signed-rank test) (Figure 4B, right). We reanalyzed the sample response in the DMS task using the same set of neurons across the two tasks (n = 50). The response was still significantly positive in the DMS

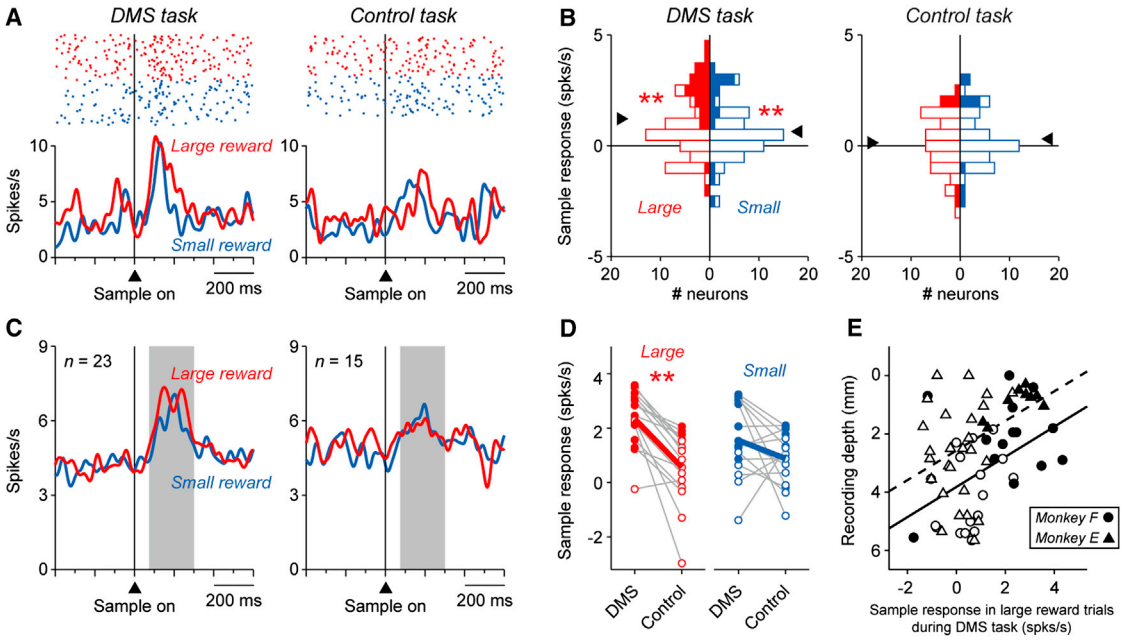

Figure 4. Response of Dopamine Neurons to the Sample Stimulus Reflecting Working Memory Demand

(A) Activity of an example dopamine neuron. Rasters and SDFs are aligned by sample stimulus onset.

(B) Distributions of the response magnitudes.

(C) Averaged activities of the 23 neurons showing a significant excitation to the sample stimulus in the DMS task (left), and 15 of the 23 neurons, which were examined using both tasks, in the control task (right).

(D) Changes in the response magnitudes of the 15 neurons between the DMS task and the control task. Double asterisk indicates a significant change ($p < 0.01$, Wilcoxon signed-rank test).

(E) Relation between the recording depth and the response magnitude to the sample stimulus in the large reward trials during the DMS task. Conventions are the same as in Figure 3.

See also Figures S2, S4B, and S6.

task ($p < 0.01$, Wilcoxon signed-rank test). Even at the single-neuron level, 23 of the 66 neurons showed a significant excitation to the sample in the DMS task (21 neurons in the large reward trials, 12 neurons in the small reward trials, and 10 neurons in both of them) ($p < 0.05$, Wilcoxon signed-rank test). Their averaged activity showed an excitation to the sample for each reward size (Figure 4C, left), and the magnitude of the excitation was significantly larger in the large reward trials than in the small reward trials (large reward trials, mean ± SD = 2.4 ± 1.0 spikes/s; small reward trials, mean ± SD = 1.6 ± 1.3 spikes/s; $p = 0.014$, Wilcoxon signed-rank test). Of the 23 neurons, 15 were also examined using the control task. Their averaged activity in the control showed little response to the sample (Figure 4C, right). Comparing the sample responses in the two tasks for each neuron (Figure 4D), the magnitude was significantly larger in the DMS task than in the control task during the large reward trials ($p < 0.01$, Wilcoxon signed-rank test), with a similar trend occurring during the small reward trials ($p = 0.19$, Wilcoxon signed-rank test).

The above data indicate that a group of dopamine neurons was excited by the sample if the monkey had to retain the information about the sample in working memory. The activity of these neurons only reflected the need to use the information about the sample, not the specific information to be retained in working memory as follows. First, most of the neurons (18/23) did not represent the orientation of sample bar, which was the information that the monkey had to remember ($p > 0.05$, two-way ANOVA). Second, these neurons responded to the sample only phasically and did not show a persistent activation that would be necessary to retain the information during the delay period (Figure S2). These response patterns make a striking contrast with the object-selective and persistent firing of dorsolateral prefrontal neurons that have long been implicated in working memory (Rao et al., 1997; Wilson et al., 1993).

We found that only a subset of dopamine neurons signaled the sample information. The next question is whether these dopamine neurons excited by the sample are scattered over the SNc and VTA or are clustered in particular regions of the structures. To address this issue, we reconstructed the recording sites of the 31 dopamine neurons in monkey F in relation to the response to the sample (Figure 2A). Neurons showing a significant excitation (indicated by red circles) tended to be located in a more dorsolateral part. To verify such topography statistically, we investigated the relation between the recording depth and the response to the sample for each monkey (Figure 4E, circles for monkey F and triangles for monkey E). As shown by the scatterplots, a significant negative correlation was observed in both monkeys (monkey F, $r = -0.47$, $p < 0.01$; monkey E,

r = −0.45, p < 0.01; Spearman's rank correlation test). This negative correlation confirmed the dorsolateral-ventromedial gradient of the sample response in dopamine neurons. It is noteworthy that this sample response makes a clear contrast with the response to the fixation point (Figure 3E). We plotted the magnitude of the fixation point response against the recording depth. The scatterplots showed no significant correlation between the response magnitude and the recording depth (monkey F, r = 0.18, p > 0.05; monkey E, r = 0.11, p > 0.05; Spearman's rank correlation test). The correlation coefficients were significantly different between the sample response and the fixation point response (monkey F, p < 0.01; monkey E, p = 0.017; Fisher's r-to-z transformation, two-tailed test). These data suggest that dopamine neuron activities at different locations reflect distinct signals.

Although dopamine neurons excited by the sample were located in a particular region, their electrophysiological properties (spike width and background firing rate) were similar to those of other dopamine neurons. There was no significant difference among them in either the spike width (p > 0.05, Wilcoxon rank-sum test) (Figure 2B, top) or the background firing rate (neurons with a significant excitation to the sample, mean ± SD = 4.5 ± 1.5 spikes/s; neurons with no significance, mean ± SD = 4.8 ± 1.3 spikes/s; p > 0.05, Wilcoxon rank-sum test).

Modulation of Dopamine Neuron Activity during Visual Search

In addition to its role in working memory, dopamine has also been implicated in attentional processing (Nieoullon, 2002), though it remains unclear what signals dopamine neurons convey to promote this process. In an attempt to address this issue, we next investigated the response of dopamine neurons to the search array in which the monkey searched a correct target by shifting attention. We modulated search difficulty by changing the search array size. If the activity of dopamine neurons reflects the cognitive demand associated with the visual search, the dopamine neurons may be most activated by the most difficult search array, for which the accuracy was reduced and the search duration was longer (Figures 1D and 1E). On the other hand, if dopamine neurons are involved in reward prediction, as a conventional theory proposes (Schultz, 1998), they should be most activated by the easiest search array, which was most likely to be performed correctly and hence followed by a reward.

We aligned dopamine neuron activity by the onset of the search array (Figure 5). An example neuron was excited by the search array in the DMS task, especially when the array was composed of two bars (two-size array) and when the large reward was expected (Figure 5A). The excitatory response decreased as the search array size increased (i.e., as the search difficulty increased). Thus, this neuron was most excited when the search array indicated the easiest search, consistent with the reward prediction theory. On the other hand, this neuron did not show such an excitation to the search array in the control task in which the search array size did not influence behavioral performance.

As a population, dopamine neurons responded to the search array in a similar manner to that of the example neuron (Figure 5B). The strongest excitation was seen in response to the two-size array in the large reward trials during the DMS task, while this excitation reduced during the control task. To systematically investigate their response to the search array, we calculated a Spearman's rank correlation coefficient between the response magnitude and the search array size for each neuron (Figure 5C). In the DMS task, the correlation was significantly negative on average in the large reward trials (p < 0.01, Wilcoxon signed-rank test), but was not significantly different from zero in the small reward trials (p > 0.05, Wilcoxon signed-rank test). This negative correlation indicates that the excitatory response decreased as the search array size increased and that this effect was robust when the large reward was expected. In the control task, on the other hand, the correlation was not significantly different from zero in either of the reward conditions (large reward trials, p > 0.05; small reward trials, p > 0.05; Wilcoxon signed-rank test). Comparing the correlation coefficients in the two tasks for each neuron (Figure 5D), the negative correlation was significantly greater in the DMS task than in the control task, especially for the large reward trials (large reward trials, p < 0.01; small reward trials, p > 0.05; Wilcoxon signed-rank test). Thus, the response to the search array was influenced by the array size if the size was associated with search difficulty.

The above data suggest that dopamine neurons were most strongly excited by the search array when it indicated the easiest search, consistent with the reward prediction theory. However, the effect of reward prediction was not homogeneously seen across dopamine neurons. We plotted, against the recording depth, the correlation coefficient between the response magnitude and the search array size for each monkey (Figure 5E, circles for monkey F and triangles for monkey E). Dopamine neurons with a strong negative correlation were observed in deeper recording sites, indicating that these neurons were located more ventromedially in the ventral midbrain. The scatterplots showed a gradient along the recording depth, and a significant negative correlation was observed in both monkeys (monkey F, r = −0.47. p < 0.01; monkey E, r = −0.50, p < 0.01; Spearman's rank correlation test). These data suggest that the reward prediction signal was transmitted mainly by ventromedially located dopamine neurons, in contrast with the sample signal that was transmitted by dorsolaterally located dopamine neurons. This was also true for the reward prediction component of the fixation point response (Figure S3).

The ventromedial dopamine neurons showing the reward prediction signal (i.e., the neurons with a significant negative correlation between the search array response and the array size) had electrophysiological properties similar to those observed in other dopamine neurons. Neither the spike width nor the background firing rate of these neurons was significantly different from that of the dorsolateral dopamine neurons responding to the sample stimulus (spike width, reward prediction neurons, mean ± SD = 0.71 ± 0.13 ms, sample responsive neurons, mean ± SD = 0.71 ± 0.13 ms, p > 0.05; background firing rate, reward prediction neurons, mean ± SD = 4.5 ± 1.1 ms, sample responsive neurons, mean ± SD = 4.5 ± 1.5 ms, p > 0.05; Wilcoxon rank-sum test).

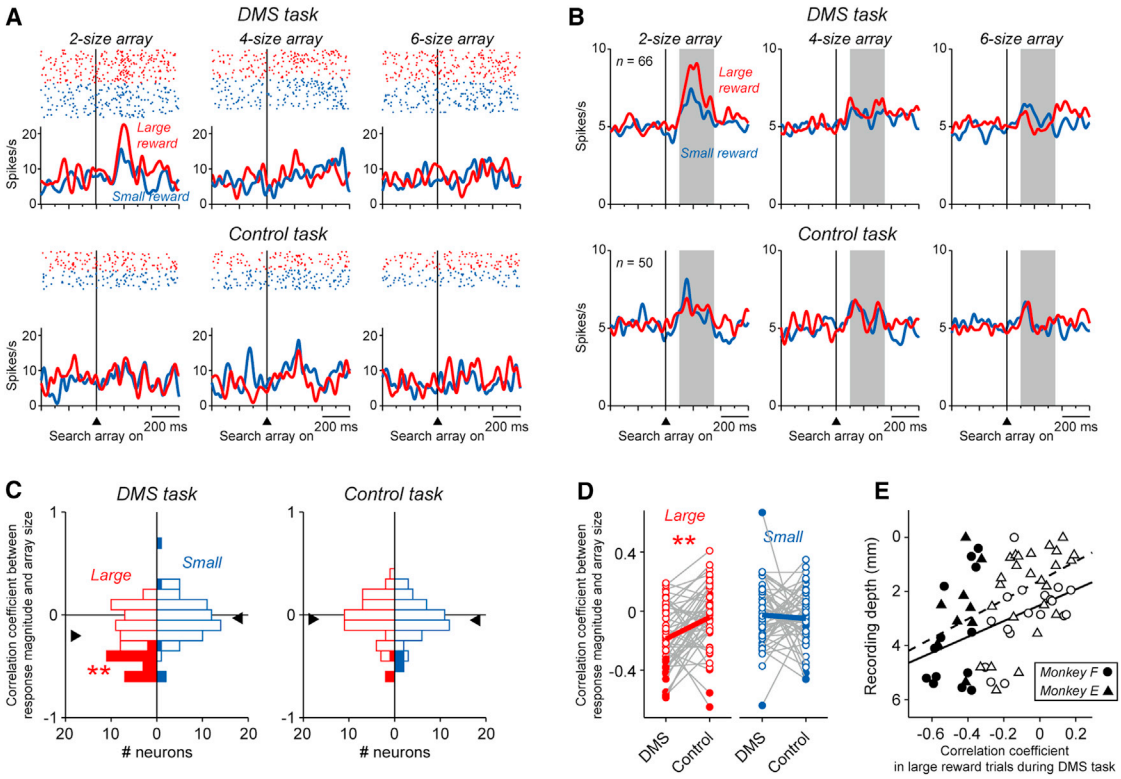

Figure 5. Response of Dopamine Neurons to the Search Array Associated with Search Difficulty

(A) Activity of an example dopamine neuron in the DMS task (top) and the control task (bottom). Rasters and SDFs are aligned by search array onset and shown for two-size array (left), four-size array (center), and six-size array (right), and are shown for the large reward trials (red) and the small reward trials (blue).

(B) Averaged activities of the 66 neurons recorded in the DMS task (top) and the 50 neurons recorded in the control task (bottom).

(C) Distributions of the Spearman's rank correlation coefficients between the response magnitude and the search array size for the 66 neurons recorded in the DMS task (left) and the 50 neurons in the control task (right). Conventions are the same as in Figure 3B.

(D) Changes in the correlation coefficients between the DMS task and the control task for each neuron recorded using both tasks (n = 50). Conventions are the same as in Figure 3D.

(E) Relation between the recording depth and the correlation coefficient in the large reward trials during the DMS task. Conventions are the same as in Figure 3E. See also Figures S4C and S7.

Modulation of Dopamine Neuron Activity when the Monkey Found a Correct Target

It has been reported that dopamine neurons are excited by biologically significant sensory events including primary reward, sensory stimuli predicting reward, and even nonrewarding sensory stimuli (Redgrave and Gurney, 2006). These excitations are caused by the external sensory stimulation and are aligned at the onset of the stimulation (we also observed dopamine responses aligned at the onset of the fixation point and at the onset of the search array in the present study). On the other hand, we here found that dopamine neurons were excited when the monkey searched out a correct target among distracters that was statically present in the display (Figure 6). This excitation was aligned by the monkey's choice behavior. Since the monkey was allowed to freely view the search array during visual search (Figure 1B), the onset of the choice was determined as the time when the monkey's eye position entered into a target window and subsequently stayed within the window to choose the target. As seen in an example neuron activity (Figure 6A) and averaged activity (Figure 6B), an excitation was observed after the choice onset, especially when the monkey found a correct target in the most difficult search (six-size array) in the large reward trials. This choice-aligned excitation occurred in the DMS task, but not in the control in which the task was just to choose a pop-out object and the correct choice rate was almost 100% (Figures 1D and 1E). This excitation occurred before external feedbacks, the chosen feedback (550 ms and 750 ms after the choice onset for monkey F and monkey E, respectively), and the reward delivery (250 ms later the chosen feedback). Therefore the choice-aligned excitation was not caused by these later sensory events. To analyze the choice-aligned excitation, we used a time window (gray area in Figure 6B) that does not contain the timing of the chosen feedback or reward delivery.

The choice-aligned excitation increased as the search array size increased. This was statistically shown by a significant positive correlation between the magnitude of the excitation and the search array size in the DMS task (large reward trials, $p < 0.01$; small reward trials, $p < 0.01$; Wilcoxon signed-rank test) (Figure 6C). Comparing the correlation coefficients in the two tasks for each neuron (Figure 6D), the correlation was significantly

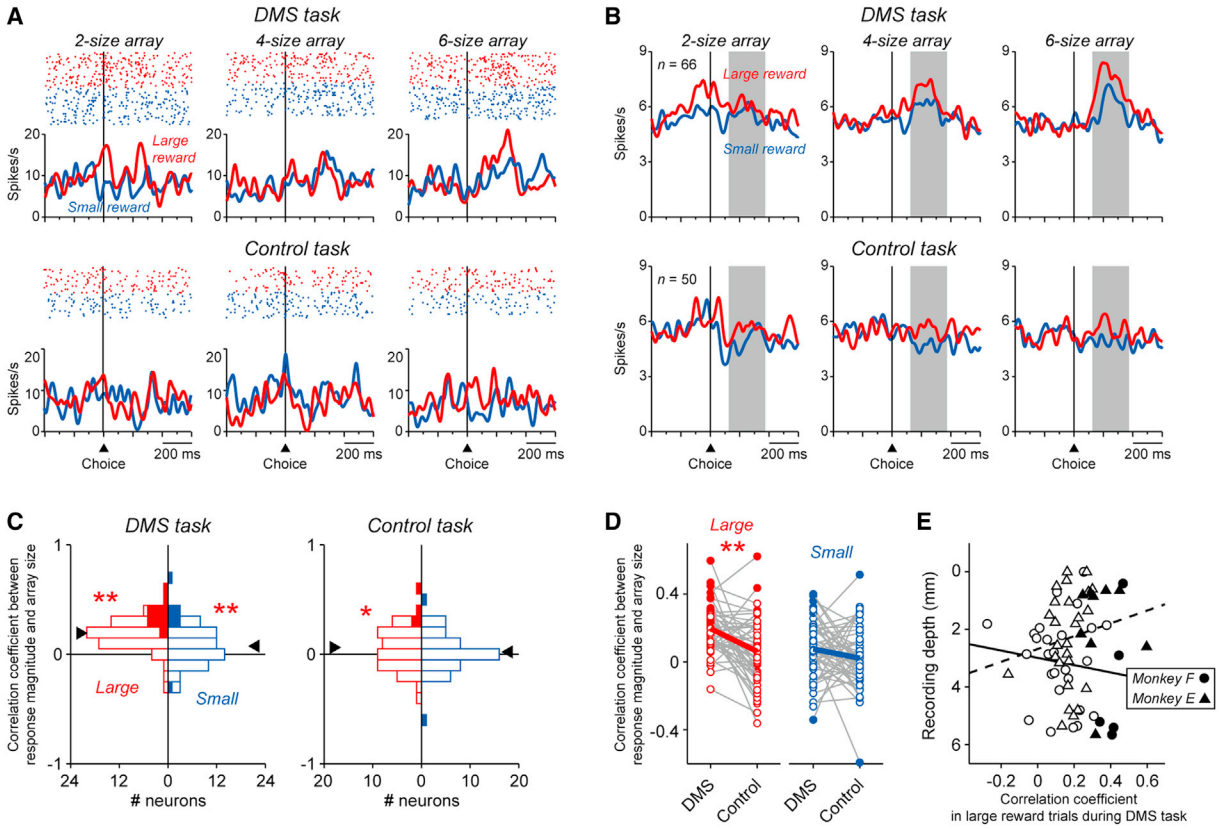

Figure 6. Choice-Aligned Response of Dopamine Neurons

(A) Activity of an example dopamine neuron. Rasters and SDFs are aligned by choice onset.

(B) Averaged activities.

(C) Distributions of the Spearman's rank correlation coefficients between the response magnitude and the search array size. Single asterisk indicates a significant deviation from zero ($p < 0.05$, Wilcoxon signed-rank test).

(D) Changes in the correlation coefficients between the DMS task and the control task.

(E) Relation between the recording depth and the correlation coefficient in the large reward trials during the DMS task. Conventions are the same as in Figure 5. See also Figures S4D and S8.

greater in the DMS task than in the control task, especially for the large reward trials (large reward trials, $p < 0.01$; small reward trials, $p > 0.05$; Wilcoxon signed-rank test). These data suggest that the choice-aligned excitation was enhanced when the monkey found a correct target in the difficult search condition and when the large reward was expected.

The choice-aligned excitation was observed even in error choice trials in which the monkey chose a wrong object (i.e., nontarget distracter) (Figure 7A). The averaged activity was aligned by the onset of the choice behavior in which the monkey chose a wrong object in the six-size array condition. The magnitude of this excitation was significantly larger than zero in both the large reward trials (mean ± SD = 1.4 ± 4.1 spikes/s, $p < 0.01$, Wilcoxon signed-rank test) and the small reward trials (mean ± SD = 2.0 ± 4.5 spikes/s, $p < 0.01$, Wilcoxon signed-rank test). Thus, these neurons would be excited when the monkey identified an object as a correct target, even if it was not actually the correct target. Consistent with this idea, no excitation was observed when the monkey temporarily looked at a nontarget distracter and subsequently changed his gaze to choose another object (Figure 7B). The averaged activity was aligned by the time when monkey's eye position entered into a nontarget window (distractor window), subsequently stayed in the window for more than 100 ms, and then went to another window. The averaged activity is shown for two cases: one for the last eye entrance before final choice (Figure 7B, right), and one for the second last eye entrance before final choice (Figure 7B, left). In either case, significant excitation or inhibition was not observed (last before final choice, large reward trials, mean ± SD = 0.4 ± 2.2 spikes/s, $p > 0.05$, small reward trials, mean ± SD = −0.2 ± 2.6 spikes/s, $p > 0.05$; second last before final choice, large reward trials, mean ± SD = 0.0 ± 3.7 spikes/s, $p > 0.05$, small reward trials, mean ± SD = −0.3 ± 2.8 spikes/s, $p > 0.05$; Wilcoxon signed-rank test). These data suggest that the choice-aligned excitation of dopamine neurons reflected the monkey's internal judgment that a chosen object was correct, rather than external sensory information provided by the chosen object.

In contrast to the sample response (Figure 4E) and the search array response (Figure 5E), dopamine neurons showing

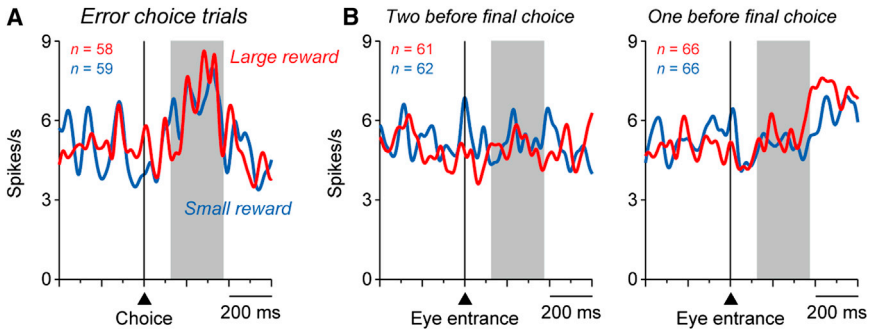

Figure 7. Choice-Aligned Response in Error Choice Trials

(A) Averaged activity aligned by error choice onset in the six-size array, large (red) and small (blue) reward trials during the DMS task. Neurons with enough error choice trial data are comprised in the sample used for this analysis (n = 58 and 59 in the large and small reward trials, respectively).

(B) Averaged activity aligned by the last eye entrance before final choice (right) (n = 66 in both the large and small reward trials) and the second last before final choice (left) (n = 61 and 62 in the large and small reward trials, respectively). Conventions are the same as in (A).

the choice-aligned excitation were observed independent of the recording depth. We plotted, against the recording depth, the correlation coefficient between the response magnitude and the search array size for each monkey (Figure 6E, circles for monkey F, and triangles for monkey E). There was no significant correlation between the recording depth and the correlation coefficient for either of the monkeys (monkey F, $r = 0.15$, $p > 0.05$; monkey E, $r = -0.19$, $p > 0.05$; Spearman's rank correlation test).

Relationship between the Responses

So far, we have shown the responses to the fixation point, sample object, search array, and monkey's choice. However, not all dopamine neurons responded to these events uniformly. For example, the response to the sample was observed in a subset of dopamine neurons. Therefore, it is possible that different groups of dopamine neurons responded to particular types of events. To test this possibility, we next examined the relationships between the responses by comparing their magnitudes for each combination (Figure 8). The response magnitudes to the fixation point, search array, and monkey's choice were positively correlated with each other (Figures 8A–8C). The correlation was significantly positive between the fixation point response and the search array response ($r = 0.55$, $p < 0.01$, Spearman's rank correlation test) (Figure 8A) and between the fixation point response and the choice-aligned response ($r = 0.37$, $p < 0.01$, Spearman's rank correlation test) (Figure 8B), though it failed to achieve a significant level between the search array response and the choice-aligned response ($r = 0.21$, $p = 0.091$, Spearman's rank correlation test) (Figure 8C). In contrast, the response magnitude to the sample was not significantly correlated with either of them (sample versus fixation point, $r = -0.018$, $p > 0.05$; sample versus search array, $r = -0.21$, $p > 0.05$; sample versus choice-aligned, $r = -0.18$, $p > 0.05$) (Figures 8D–8F). These observations might suggest the possibility that the sample response of dopamine neurons was generated by a different mechanism from that inducing the other responses.

DISCUSSION

Using the DMS task, we found that dopamine neurons responded to several types of task events that were associated with distinct cognitive operations. A group of dopamine neurons responded to the sample stimulus if the monkey was required to attend to that stimulus and store it in working memory. These neurons were located dorsolaterally in the SNc. On the other hand, dopamine neurons that were located more ventromedially represented reward prediction signals, responding to the fixation point predicting reward magnitude and the search array indicating task difficulty. Dopamine neurons in a more widespread region were excited when the monkey found a correct target among distractors.

Our data suggest that the excitatory response to the sample stimulus reflected the behavioral relevance associated with the cognitive processing induced by the stimulus. Since dopamine neurons are well known to be excited by sensory stimuli predicting the size (Tobler et al., 2005) and probability (Fiorillo et al., 2003) of reward, it might be argued that the sample stimulus could act as a reward predictor and accordingly evoked the excitatory response in dopamine neurons. However, the sample stimulus did not actually provide any information about the size or probability of future reward. Dopamine neurons are also known to be excited by sensory stimuli predicting the timing of reward, such as fixation point (Bromberg-Martin et al., 2010a; Takikawa et al., 2004) and task instruction (Schultz et al., 1993) presented at the beginning of a trial. Although the sample might predict the timing of an upcoming reward, it induced no excitation in the control task in which the sample was also predictive of the timing. Thus reward prediction cannot fully account for the excitatory response to the sample stimulus.

On the other hand, some dopamine neurons are also known to be excited by sensory stimuli that are not directly associated with reward (Bromberg-Martin et al., 2010b; Horvitz, 2000; Redgrave and Gurney, 2006). For instance, recent studies have reported that a group of dopamine neurons is excited not only by rewarding stimuli but also by aversive stimuli such as air puffs and tail pinches (Brischoux et al., 2009; Guarraci and Kapp, 1999; Matsumoto and Hikosaka, 2009). These neurons are presumed to represent motivational salience, which indicates a quantity that is high for both rewarding and aversive events and is low for motivationally neutral events (Matsumoto and Hikosaka, 2009). In primates, these neurons are located in the dorsolateral SNc, while dopamine neurons in the ventromedial SNc and the VTA represent a conventional reward value signal (Matsumoto and Hikosaka, 2009). It should be mentioned here that the distribution of the dopamine neurons signaling the motivational salience overlaps with that of the dopamine neurons responding to the sample stimulus in our DMS task (please note that we did not test whether single dopamine neurons represent

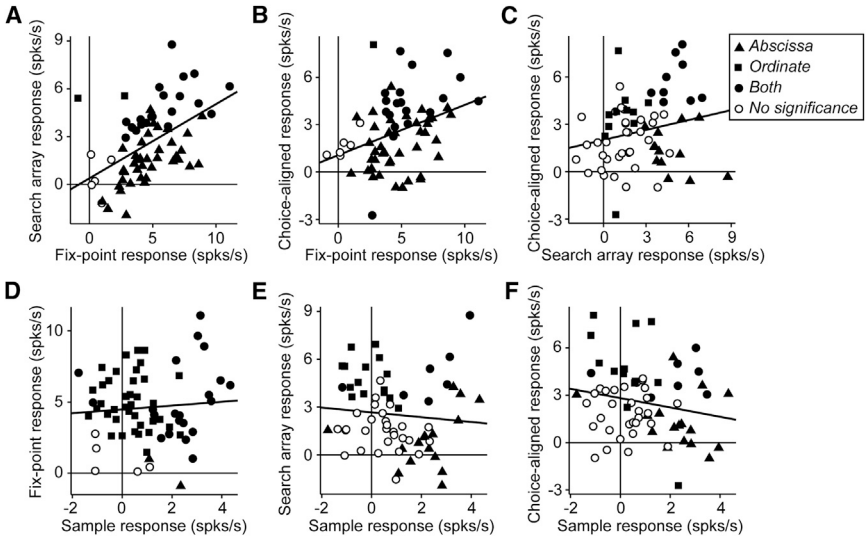

Figure 8. Comparison between the Responses

(A) Search array response versus fixation point response.

(B) Choice-aligned response versus fixation point response.

(C) Choice-aligned response versus search array response.

(D) Fixation point response versus sample response.

(E) Search array response versus sample response.

(F) Choice-aligned response versus sample response. The fixation point response and the sample response were collected in the large reward trials during the DMS task. The search array response was collected in the two-size array, large reward trials during the DMS task. The choice-aligned response was collected in the six-size array, large reward trials during the DMS task. Filled triangles, filled squares, and filled circles indicate neurons with significant responses along abscissa, ordinate, and both, respectively (Wilcoxon signed-rank test, $p < 0.05$). Open circles, no significance. Line indicates regression line.

both signals). Since the sample stimulus is also "salient" in a cognitive aspect, dopamine neurons in the dorsolateral SNc may represent salience regardless of motivational or cognitive. Further studies are called for to examine whether the same dopamine neurons represent the two types of salience at the single neuron level.

Previous studies reported that dopamine neurons are also excited by intense sensory stimuli, such as loud click sounds and large pictures immediately presented in front of animals (Horvitz, 2000; Horvitz et al., 1997; Steinfels et al., 1983). These responses are assumed to represent physical, novelty, or surprising salience (Schultz, 2013) and seem to reflect the extent to which the stimulus captures attention that is automatically driven in a "bottom-up" fashion. On the other hand, the sample stimulus in our DMS task captured attention that was volitionally driven by a "top-down" process because the monkey had to store the sample in working memory. In the field of visual neuroscience, it has long been investigated how these two distinct attentional processes influence neuronal activity in the visual cortical system (Kastner and Ungerleider, 2000; Sarter et al., 2001; Treue, 2001). Yet, it remains to be determined whether dopamine signals are affected by the bottom-up and top-down processes in an integrated manner or treat the two attentional processes as independent.

In contrast to the response to the sample stimulus, the responses to the fixation point and the search array were related to reward prediction. These excitatory responses were stronger when the fixation point predicted the large reward and when the search array indicated easy search (i.e., high reward probability and short delay until reward delivery). Previous studies have also shown that dopamine neurons respond to reward-predicting stimuli in a similar way. This response reflects the size (Tobler et al., 2005), probability (Fiorillo et al., 2003), and delay (Fiorillo et al., 2008; Kobayashi and Schultz, 2008) of the predicted reward in a manner that matches behavioral preferences, such as large reward over small ones, probable reward over improbable ones, and immediate reward over delayed ones. These dopamine signals have been thought to represent reward prediction error that is evoked when ongoing events are better than expected.

We next found that dopamine neurons were excited when the monkey found a correct target among distracters. This excitation was aligned by the monkey's choice behavior. Notably, this choice-aligned excitation was modulated by the search difficulty in a manner opposite to the search array response. Whereas dopamine neurons showed the strongest search array response in the easiest search condition, they exhibited the strongest choice-aligned excitation in the most difficult search condition. These complementary responses would be in parallel with reward prediction error. When a two-size array was presented (i.e., the easiest search condition), a reward was predicted with a higher probability than when a four- or six-size array was presented. This is the time when a positive prediction error is evoked and when the strongest search array response was observed. On the other hand, when the monkey found a correct target in a six-size array (i.e., the most difficult search condition), the animal would obtain a reward that was less secured than in the two- and four-size array conditions. This is the time when a positive prediction error is evoked and when the strongest choice-aligned excitation was observed.

The search array response and the choice-aligned excitation were weaker in the control task than in the DMS task. This effect could also be explained by reward prediction error coding. In the control, the correct choice rate was almost 100% and was not influenced by the search array size. Therefore, the monkey would always expect a reward with the high probability regardless of whether a two-, four-, or six-size array was presented. Thus, zero prediction error was evoked even if a two-size array was presented and even if the monkey found a correct target in a six-size array. This could account for why dopamine neurons

showed the weaker search array response and the weaker choice-aligned excitation in the control task. Since the search array response in the control was not completely zero (though it was not significant), the monkey might somewhat confuse the two tasks that ran in separate blocks.

Although dopamine neurons are known to respond to physical sensory stimulation, the choice-aligned excitation reflected the monkey's internal judgment rather than external sensory information provided by a chosen object. That is, the choice-aligned excitation occurred even in error choice trials in which the monkey identified a wrong object as a correct target. A recent study of another laboratory reported that dopamine neuron activity reflected the subjective experience but not the physical presence of sensory stimuli (de Lafuente and Romo, 2011). They recorded dopamine neuron activity in monkeys performing a perceptual detection task in which the animal had to indicate the presence or absence of a somatosensory stimulus. They found that dopamine neurons were activated by the stimulus only when the monkey reported its presence, whereas they were not activated by the same physical stimulus when the animal reported its absence. Together with our findings, these recent data suggest that dopamine signals are triggered by internally arising experiences rather than external sensory stimulation per se.

We note that dopamine neurons at different locations responded to distinct task events (see Figure S4 for a further analysis supporting the regionally distinct dopamine signals). Their distributions provide important insights into downstream structures for each dopamine signal. We found that dopamine neurons in the dorsolateral SNc were excited by the sample stimulus. In primates, dopamine neurons around this region have been shown to project to the dlPFC rather than the ventral and medial prefrontal cortex (vmPFC) (Porrino and Goldman-Rakic, 1982; Williams and Goldman-Rakic, 1993). Thus, the excitatory sample signal would be provided to the dlPFC that is well known for its crucial roles in working memory. The same dopamine signal may be transmitted to the dorsal striatum that receives dopaminergic projections from the dorsolateral SNc (Haber et al., 2000; Lynd-Balta and Haber, 1994). Recent studies have revealed that the dopaminergic input to the dorsal striatum is also involved in working memory and orienting attention (Cools, 2011; Hikosaka et al., 2006; Landau et al., 2009).

In contrast with dopamine neurons in the dorsolateral SNc, more ventromedially located dopamine neurons responded to the fixation point and the search array in a manner corresponding to reward prediction error coding. These neurons were distributed around the ventromedial SNc and the VTA that project to the vmPFC, including the anterior cingulate cortex (ACC) and the orbitofrontal cortex (OFC) (Porrino and Goldman-Rakic, 1982; Williams and Goldman-Rakic, 1993). These cortical areas have been implicated in reward value coding (Kennerley et al., 2011; Morrison and Salzman, 2009; Roesch and Olson, 2004) and value-based decision-making (Gläscher et al., 2009). Dopamine neurons may provide the vmPFC with the reward-related signal, such as the size and probability of future reward. The same dopamine signal would be transmitted to the ventral striatum including the nucleus accumbens (NAc) that receives dopaminergic inputs from the ventromedial SNc and the VTA (Haber et al., 2000; Lynd-Balta and Haber, 1994). Such dopaminergic inputs to the NAc play crucial roles in regulating reward-related behaviors (Faure et al., 2008).

Dopamine neurons with the choice-aligned excitation, signaling monkey's judgment about whether they chose a correct target or a wrong distracter, were observed in a more widespread region of the ventral midbrain. Thus, this signal would be transmitted to relatively extensive brain areas (Williams and Goldman-Rakic, 1998). One major candidate may be the ACC, which has been implicated in performance monitoring (Ridderinkhof et al., 2004). The choice-aligned signal about monkey's judgment would be useful for the ACC to monitor the monkey's choice behavior. Indeed, injection of dopamine antagonists reduces a neural signal associated with performance monitoring in the ACC (Vezoli and Procyk, 2009).

As described above, we suggested the possible downstream structures for each dopamine signal. However, it still remains to be determined what roles the dopamine signals play in promoting cognitive processes in these structures. Although we analyzed the correlation between the response magnitude and behavioral performance for each signal, no or only a slight correlation was detected (see Figure S5 for the fixation point response, Figure S6 for the sample response, Figure S7 for the search array response, and Figure S8 for the choice-aligned response). Further studies are necessary to elucidate the functional contributions of the distinct dopamine signals that would be transmitted to different downstream structures.

In summary, we found that dopamine neurons at different locations responded to cognitive events in distinct manners. These dopamine signals are roughly divided into two types. One signal reflected the cognitive processing induced by the sample stimulus. This type of signal represented the cognitive significance of the stimulus, not the specific information to be retained in working memory. The other signal was consistent with reward prediction error. This type of signal would be triggered by internally arising experiences rather than external sensory stimulation per se. It is important to note that the difference between the two groups was gradual, not distinct, along the dorsolateral-ventromedial axis of the ventral midbrain. Our findings suggest an anatomical gradient of dopamine signals suitable for different functions.

EXPERIMENTAL PROCEDURES

Animals

Two adult rhesus monkeys (*Macaca mulatta*; monkey E, male, 7.0 kg; monkey F, male, 7.8 kg) were used for the present experiments. All procedures for animal care and experimentation were approved by the Institutional Animal Care and Use Committee of Primate Research Institute, Kyoto University (permission number 2010-080) and were complied with the Guidelines for Care and Use of Nonhuman Primates by Primate Research Institute, Kyoto University (2010).

Behavioral Task

Behavioral task events and data acquisition were controlled by TEMPO system (Reflective Computing). The monkeys sat in a primate chair facing a frontoparallel computer monitor in a sound-attenuated and electrically shield room. Eye movements were monitored using an infrared eye-tracking system (Eyelink, SR Research) by sampling at 500 Hz.

The monkeys performed a DMS task (Figure 1A). Trials began with the appearance of a central, colored fixation point (0.5° diameter), and the animal

was required to fixate the point. The color of the fixation point indicated the magnitude of a liquid reward that the monkey would obtain after correct performance on the trial (red indicated 0.27 ml large reward and blue indicated 0.03 ml small reward for monkey E; blue indicated 0.27 ml large reward and red indicated 0.06 ml small reward for monkey F). After 750 ms of fixation, the colored fixation point disappeared, and a tilted bar was presented as a sample at the center of the monitor for 750 ms. Then the sample bar was removed and a white fixation point appeared during a delay period of 750 ms. The monkey had to maintain fixation until the end of the delay period. After that, the fixation point disappeared, and a visual search array that was composed of two, four, or six bars with different orientations, one of which matched the sample bar, was presented (6° eccentricity for monkey E and 6° or 7.5° for monkey F). The monkey was required to find the matching target within a time limit (1,500 ms for monkey E and 1,300 ms for monkey F). No constraints were placed on eye position during search behavior so that the monkey could make several saccades (Figure 1B). The monkey needed to choose the matching target by fixating it for a certain period (750 ms for monkey E and 550 ms for monkey F). The fixation was required within a ±2.5° window. After the choice, nonchosen bars were removed, and only the chosen bar was kept on for 250 ms, during which the monkey still had to keep fixating the matching target. Then correct choice was signaled by a tone, and simultaneously a liquid reward of which the magnitude was indicated earlier was delivered. If the monkey chose a nontarget, incorrect object, it was signaled by a beep tone. All trials were presented with a random intertrial interval that averaged 3 s (2.5–3.5 s) for monkey E and 2.5 s (2–3 s) for monkey F.

The tilted bars were 0.7° of visual angle in width and 2.1° in length for monkey E, and 0.7° in width and 1.4° in length for monkey F. Their orientations were 20°–170° with a step of 30°.

The sample was behaviorally relevant in the DMS task, whereas it was made irrelevant in a control task (Figure 1C). Its task procedure was the same as that of the DMS task except for the search array. In the control, the search array was composed of two to six objects: one of them was a triangle and the others were circles for monkey E, and one of them was a horizontal bar and the others were circles for monkey F. These objects had the same area size with the tilted bars in the DMS task. The monkey was required to choose the pop-out triangle or horizontal bar regardless of what the sample was.

These two tasks were run in separate blocks of approximately 60–80 trials and were interleaved with each other. For each neuron, we collected data by repeating the two tasks twice or more if possible. Changing the order of the tasks resulted in the same conclusions.

Electrophysiology

A plastic head holder and recording chamber were fixed to the skull under general anesthesia and sterile surgical conditions. The recording chamber was placed over the frontoparietal cortex, tilted laterally by 36°, and aimed at the SNc and the VTA. The head holder and the recording chamber were embedded in dental acrylic that covered the top of the skull and were connected to the skull using plastic screws.

Single-unit recordings were performed using tungsten electrodes with impedance of 0.5–2.0 MΩ (Frederick Haer) that were advanced by an oil-driven micromanipulator (MO-97-S, Narishige). The recording sites were determined using a grid system, which allowed recordings at every 1 mm between penetrations. The electrode was introduced into the brain through a stainless steel guide tube which was inserted into one of the grid holes and then into the brain via the dura. For finer mapping of neurons, we also used a complementary grid which allowed electrode penetrations between the holes of the original grid.

Single-unit potentials were amplified and band-pass filtered (100 Hz to 8 kHz) using a multichannel processor (MCP Plus 8, Alpha Omega) and isolated online using a voltage-time window discrimination system (ASD, Alpha Omega). The time of occurrence of each action potential was stored with 1 ms resolution.

Data Analysis

We evaluated behavioral performance by correct choice rate and choice latency. Correct choice rate was determined by $N_{target}/(N_{target} + N_{distractor}) \times 100$, where N_{target} is the number of trials in which the monkey chose a matching target correctly, and $N_{distractor}$ is the number of trials in which the monkey chose a wrong distractor. Choice latency was determined as the time interval between the onset of the search array and the time when the monkey's eye position entered into a target window and subsequently stayed within the window to choose the target.

To analyze neuron activity, we combined data from both monkeys because they were qualitatively identical for our major findings. We defined the response to the fixation point as the discharge rate during 75–325 ms after the fixation point onset minus the discharge rate during 300–0 ms before the onset. The response to the sample stimulus was defined as the discharge rate during 75–300 ms after the sample stimulus onset minus the discharge rate during 300–0 ms before the onset. The response to the search array was defined as the discharge rate during 100–350 ms after the search array onset minus the discharge rate during 300–0 ms before the onset. The choice-aligned response was determined as the discharge rate during 125–375 ms after the choice onset minus the discharge rate during 300–0 ms before the onset. The choice onset was determined as the time when the monkey's eye position entered into a target window and subsequently stayed within the window to choose the target. These time windows were determined on the basis of the averaged activity of dopamine neurons. Specifically, we set the time windows such that they include major parts of the responses.

To calculate spike density functions (SDFs), each spike was replaced by a Gaussian curve (σ = 15 ms).

Histology

At the end of the recording session in monkey F, we selected representative locations of electrode penetration and made electrolytic microlesions (14 μA and 40 s). Then monkey F was deeply anaesthetized with pentobarbital sodium and perfused with 10% formaldehyde. The brain was blocked and equilibrated with 30% sucrose. Frozen sections were cut every 50 μm in the coronal plane. The sections were immunostained for tyrosine hydroxylase (TH; mouse anti-TH antibody, 1:1,000, Millipore; biotin-SP donkey anti-mouse IgG, 1:1,000, Jackson) and counterstained with neutral red.

SUPPLEMENTAL INFORMATION

Supplemental Information includes eight figures and can be found with this article at http://dx.doi.org/10.1016/j.neuron.2013.07.002.

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